AN ALTERNATIVE CISPLATIN BASED INDUCTION CHEMOTHERAPY DOSING REGIMEN IN ADVANCED ESOPHAGEAL EPITHELIAL CANCERS.

-A SINGLE ARM CROSS SECTIONAL STUDY-

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CERTIFICATE

This is to certify that **Dr. VIVEK. R. S** has been a D.M Post Graduate Student between July 2007 and August 2010 in the Department of Medical Oncology, Madras Medical College, Chennai.

This dissertation titled **"An Alternative Cisplatin based Induction Chemotherapy dosing regimen in advanced esophageal epithelial cancers"** is a bonafide work done by him during the study period and is being submitted to the Tamil Nadu Dr.M.G.R Medical University in partial fulfillment of the Branch VII D.M- MEDICAL ONCOLOGY Examination.

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AN ALTERNATIVE CISPLATIN BASED INDUCTION CHEMOTHERAPY DOSING REGIMEN IN ADVANCED ESOPHAGEAL EPITHELIAL CANCERS.

INTRODUCTION

INTRODUCTION

Esophageal cancer is unique among the gastrointestinal tract malignancies because it embodies two distinct histopathologic types, squamous cell carcinoma and adenocarcinoma. In 2008, an estimated 16,470 people in the United States were told that they have esophageal carcinoma[1]. During the same year, an estimated 14,280 people died of this disease[1]. This high rate of mortality occurs even though the esophagus is in a relatively accessible location and the use of screening endoscopy is widespread.

One reason for the high mortality is the difficulty in properly identifying and treating early lesions. Which type of cancer occurs in a given patient or predominates in a given geographic area depends on many variables, including individual lifestyle, socioeconomic pressures, and environmental factors. The United States, along with many other Western countries, has witnessed in recent decades a profound increase in incidence rates of adenocarcinoma, whereas squamous cell carcinoma continues to predominate worldwide.

Although it would seem appropriate to individualize treatment of these tumors, often they are managed as a single entity. Present-day therapeutic interventions have had limited impact on survival, as evidenced by the case fatality rate of 90%. However, a more thorough understanding of the initiating events, the molecular biologic basis, and treatment successes and failures has

begun to spawn a new era of therapy aimed at targeting both adenocarcinoma and squamous cell carcinoma of the esophagus.

At the department of Medical Oncology, Madras Medical College, Chennai, we register about 2200-3000 new patents annually. Of these, nearly 4-6% cancers are those, which involve the esophagus as their primary site. Most of the cancers are Squamous cell carcinomas, while Adenocarcinomas have been showing a steady increase over the past few decades.

Natural history data and patterns of failure after specific treatment modalities provide insight into the biologic behavior of esophageal carcinoma and suggest potential therapeutic avenues to explore. At presentation, the overwhelming majority of patients have locally or regionally advanced or disseminated cancer, irrespective of histologic type[1,2].

The lack of a serosal envelope and the rich submucosal lymphatic network of the esophagus provide a favorable milieu for extensive local infiltration by tumor and lymph node involvement. If distant disease is not clinically evident at the time that patients are initially diagnosed with esophageal carcinoma, evidence suggests that occult micrometastases are invariably present, and recurrence patterns confirm that distant failure is a significant and universally fatal component of relapse[3,4,5,6,7].

While patients diagnosed with a deeply invasive carcinoma are usually treated with chemotherapy and radiation followed by surgery, many patients with early lesions are today managed endoscopically.

Median survival after esophagectomy for patients with localized disease is 15 to 18 months with a 5-year overall survival rate of 20% to 25%. Patterns of failure after esophagectomy suggest that both location of tumor and histologic type may influence the distribution of recurrence. In patients with cancers of the upper and middle thirds of the esophagus, which are predominately squamous cell carcinomas, locoregional recurrence predominates over distant recurrence, whereas in patients with lesions of the lower third, where adenocarcinomas are more frequently located, distant recurrence is more common[3,4]. The addition of chemotherapy, radiotherapy, or chemoradiotherapy to surgery may alter patterns of failure, although reported results are not consistent.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Optimal treatment of esophageal cancer in every major stage grouping (premalignant or intramucosal lesions, localized resectable tumors, and unresectable metastatic disease) remains elusive and a work in progress that continues to engender substantial controversy. The paucity of appropriately designed studies to scientifically determine the most effective therapeutic strategy for any given clinical situation fuels the ongoing debate and undermines the potential for achieving consensus. Although there is no disagreement that esophageal resection prevents progression from high-grade dysplasia to invasive carcinoma and is curative for T1 lesions limited to the mucosa, the morbidity and mortality associated with esophagectomy has created enthusiasm for alternative approaches such as mucosal ablation and endoscopic resection. Surgery has always been considered the most effective way of ensuring both locoregional control and long-term survival for patients with tumors invading into or beyond the submucosa with or without lymph node involvement. Some investigators suggest that extending the limits of resection will further improve outcome. However, surgery alone or any other single modality fails in most patients, which has led many oncologists to embrace combined modality therapy and some to question the necessity for surgical intervention. Chemoradiotherapy with or without resection is the most common therapeutic regimen offered to patients with esophageal carcinoma in the United States[2]. A full understanding of these issues and others regarding the treatment of carcinoma of the esophagus

requires careful scrutiny of the available literature with an attempt to separate bias from fact in developing a rational therapeutic approach for patients regardless of the stage of their disease. Here, we shall discuss the role of chemotherapy, especially cisplatin based regimens, in both locally advanced and metastatic esophageal carcinoma.

CHEMOTHERAPY IN LOCALLY ADVANCED DISEASE

For locally advanced esophageal cancer, surgery remains the mainstay of treatment. Various reviews have reported 5-year overall survival(OS) rates from 10% up to 30% to 40% with surgical resection alone[8,9]. Primary radiation therapy previously was used for local tumor control, although less successfully. In one large series, the 3-year survival after radiotherapy alone was only 6%[8]. For metastatic disease, chemotherapy alone results in response rates of only 20% to 40% and median survivals of 8 to 10 months[9].

Given the activity of all three modalities, numerous studies have combined them in Distinct neoadjuvant(preoperative) strategies for locally advanced disease. Multimodality approaches have included chemotherapy or concurrent chemoradiotherapy followed by surgery or definitive chemoradiotherapy, in an effort to improve the dismal prognosis of this

aggressive cancer. Relatively few studies have focused on an adjuvant (postoperative) approach.

The results of these studies have been mixed, and their combined outcomes have failed to elevate any preoperative strategies to a clear standard for resectable esophageal cancer. Recent trials involving preoperative chemoradiotherapy and pre- and peri-operative chemotherapy, however, have demonstrated improved survival over surgery alone. Based on these data, many clinicians now treat locoregional disease with preoperative multimodality therapy.

A. NEOADJUVANT CHEMOTHERAPY

Despite the short-lived responses using chemotherapy alone in advanced disease, neoadjuvant chemotherapy is associated with many theoretical benefits[10]. This approach has the potential to assess tumor response to chemotherapy and direct the possible use of chemotherapy postoperatively. Chemotherapy also may improve baseline dysphagia, downstage the primary tumor, and increase resection rates and treat micrometastatic disease that is undetectable at diagnosis. Kok and colleagues[11] reported a small randomized phase three trial, in which 148 patients who had SCC were randomized to surgery alone or preoperative cisplatin/ etoposide

followed by surgery. Preoperative chemotherapy was associated with a significant improvement in median OS (18.5 months versus 11 months). No final report of this study has been published.

The large North American Intergroup 113 trial, however, failed to show a survival benefit for peri-operative cisplatin/5-fluorouracil (5-FU) plus surgery compared with surgery alone in 440 patients who had adenocarcinoma and squamous cell carcinoma[12]. Patients in the combined-modality arm received three cycles of cisplatin/5-FU preoperatively and two cycles postoperatively. Pathologic complete responses (pCR) were seen in only 2.5% of patients receiving preoperative chemotherapy, and there was no improvement in the curative resection rate. The median OS was not significantly different in the two groups, and the 5-year OS with or without chemotherapy was 20%. The addition of chemotherapy did not change the rate of recurrence either locally or at distant sites. Outcome also did not differ by histology, with no benefit seen for preoperative chemotherapy for either adenocarcinoma or SCC.

Renewed interest in preoperative chemotherapy was generated by a trial performed by the Medical Research Council Esophageal Cancer Working Group[13]. This study randomized 802 patients (nearly double the number of patients in the Intergroup trial) to surgery alone versus two cycles of preoperative cisplatin/5-FU. At a relatively short median follow-up of only 2

years, the chemotherapy-treated group demonstrated improved median OS (16.8 months versus 13.3 months) and 2-year survival (43% versus 34%). The curative resection rate was improved marginally from 55% to 60%, and the pCR rate was 4% in the preoperative therapy group. Mature results of this trial recently were updated in abstract form[14]. At 5 years, there continued to be a statistically significant but numerically smaller OS benefit for preoperative therapy (23% versus 17%). The trial reported a sobering operative mortality rate of 10%.

It may be that the larger sample size compared with the Intergroup trial facilitated the detection of a small improvement with chemotherapy. In addition, a larger proportion of patients on this trial had adenocarcinoma histology compared with the Intergroup 113 trial (66% versus 54%). Two recent meta-analyses (described in detail) suggest a potentially greater survival benefit from preoperative chemotherapy for patients who have adenocarcinoma versus SCC[15,16].

Additional evidence to support the use of peri-operative chemotherapy comes from the recent Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial performed in the United Kingdom[17]. This trial randomized 503 patients who had gastric or gastroesophageal (GE) junction adenocarcinoma to three cycles each of pre-and postoperative ECF

(epirubicin/ cisplatin/ infusional 5-FU) chemotherapy and surgery or surgery alone. peri-operative chemotherapy resulted in significant improvement in 5-year OS (36% versus 23%). There was no improvement, however, in the curative resection rate, and there were no cases of pCR. Although only 26% of patients on this trial had tumors in the GE junction and lower esophagus, the results still may apply to esophageal cancer.

Finally, data from the French FFCD 9703 trial of 224 patients who had gastric or lower esophageal adenocarcinoma recently were presented[18]. Patients were randomized to two or three cycles of preoperative cisplatin/5-FU followed by surgery versus surgery alone. Those patients who appeared to benefit clinically or radiographically from preoperative therapy or who had persistent T3 or node-positive disease at surgery also received an additional three or four cycles of chemotherapy. Preoperative chemotherapy was associated with a significant improvement in R0 resection rate (84% versus 73%), 5-year disease-free survival (DFS, 34% versus 21%) and 5-year OS (38% versus 24%). Although comparisons between different clinical trials must be made cautiously, the survival benefit seen with preoperative cisplatin/5-FU on this trial appears to be very similar to that seen with peri-operative ECF in the MAGIC trial. Because of the smaller sample size on this trial, however, outcome differences in as few as 10 to 15 patients would have changed the trial outcome. Also, the trial did not stage patients with endoscopic ultrasound consistently or

stratify them by pre therapy stage. In a small-scale trial, even a slight imbalance in pretherapy stage might impact the trial outcome.

Overall, recent trials suggest a survival benefit for preoperative chemotherapy, although preoperative chemotherapy alone is associated with a low pCR rate and inconsistent improvement in the resection rate. Such a survival benefit also was demonstrated in a recent large, individual patient data meta-analysis of 12 randomized trials involving preoperative chemotherapy[16]. This meta-analysis revealed a 5-year survival benefit of only 4% with preoperative chemotherapy, with a suggestion of lesser benefit for squamous (4%) compared with adenocarcinoma histology (7%).

B. ADJUVANT CHEMOTHERAPY

Combined-modality therapy in esophageal carcinoma long has focused on preoperative strategies. The role of adjuvant therapy has not been studied extensively, and the data that are available suggest equivocal results.

Postoperative chemotherapy without preoperative therapy was studied in two Japanese randomized trials, where patients who had SCC histology were randomized to receive two cycles of chemotherapy with cisplatin/vindesine[19] or cisplatin/5-FU[20] respectively. Although the trial with cisplatin/vindesine did not show any survival benefit, an unplanned subset

analysis of the trial with cisplatin/5-FU revealed a survival benefit for patients who had lymph node involvement (5-year DFS 52% versus 38%).

The possible benefit for postoperative therapy suggested by the previously mentioned trials led to a subsequent Japanese trial that randomized 330 patients who had SCC histology to surgery and either two cycles of pre- or postoperative cisplatin/5-FU[21]. Data recently presented in abstract form revealed that preoperative chemotherapy was associated with a significant improvement in OS compared with postoperative chemotherapy (hazard ratio [HR] 0.64, 95% CI, 0.45 to 0.91), further questioning the role of adjuvant chemotherapy for SCC. A significant number of patients on this trial, however, never received postoperative chemotherapy, making the results difficult to interpret. Another unexpected finding is that an unplanned subset analysis suggested that the benefit for preoperative therapy over postoperative therapy was seen only in patients without lymph node involvement, in contrast to the previously mentioned study where a benefit for adjuvant chemotherapy over observation was noted in patients who had lymph node involvement.

The overall lack of benefit for adjuvant chemotherapy suggested by the Japanese trials is consistent with the results of a randomized French trial, which also found no survival benefit for 6 to 8 months of adjuvant chemotherapy with cisplatin/5-FU[22]. In fact, there were significantly more complications in the chemotherapy group.

In contrast, a pilot Eastern Cooperative Oncology Group (ECOG) trial recently evaluated four cycles of postoperative paclitaxel/cisplatin in patients who had node-positive esophageal or GE junction adenocarcinoma[23]. Two-year OS was 60%, which is statistically superior compared with the historical control (38%, derived from Intergroup 113 trial).

Trials involving adjuvant radiotherapy generally have reported negative results. A French study randomized 221 patients to surgery alone versus surgery followed by radiation and found no survival benefit from radiation[24]. Another randomized study of 130 patients from Hong Kong actually demonstrated increased mortality with postoperative radiation (8.7 versus 15.2 months, in favor of the no adjuvant therapy group), with the difference attributed to radiation-related deaths and early metastatic disease[25].

Finally, a large prospective Chinese study also failed to detect an OS benefit among 495 patients randomized to adjuvant radiation or no further therapy[26]. A subgroup analysis of node-positive patients, however, did show a 5-year OS benefit favoring the radiation group (35.1% versus 13.1%).

Although trials of adjuvant radiotherapy alone have not suggested significant benefit, there may be benefit from adjuvant concurrent chemoradiotherapy, as suggested the results of the Intergroup trial 116 in gastric adenocarcinoma[27]. This trial revealed a significant improvement in OS and DFS for the delivery of postoperative therapy with 5-FU/leucovorin and radiation compared with surgery alone as a relatively modest 20% of the patients

treated had proximal gastric cancers (with involvement of the GE junction) and primary GE junction cancers, these data may justify the use of postoperative therapy in such patients who have not received preoperative therapy. It should be noted that the results of this trial have been questioned because of the relatively inadequate surgical resections that were performed; 54% of patients had a D0 resection, which is less than a complete dissection of the involved lymph nodes. It has been argued that radiation in this setting compensated for inadequate surgery and that its benefits may not be seen if a more complete or extensive D1 or D2 surgical resection is undertaken.

C. COMBINED NEOADJUVANT CHEMORADIOTHERAPY.

Although recent pre- and peri-operative chemotherapy trials have indicated a survival benefit, the low rate of pCR and the inconsistent impact on rates of operability have led researchers to investigate neoadjuvant chemoradiotherapy.

Chemoradiotherapy typically involves regimens of cisplatin or mitomycin and continuous infusion 5-FU, with radiotherapy dosages from 30 to 40 Gy and up to 60 Gy in more recent trials. Such therapy results in pCR rates of 20% to 40%, with long-term survival of no more than 25% to 35%[28,29]. Superior survival is achieved consistently, though in patients achieving a pCR to chemoradiotherapy (up to 50% to 60% at 5 years)[30-34].

These results are at the expense of significant toxicities, primarily hematologic and gastrointestinal (GI), which have been greatest in trials employing a higher dose of or twice-daily radiation or in which radiotherapy overlapped all cycles of preoperative chemotherapy[35]. The GI toxicity associated with cisplatin/5-FU and radiation includes nausea, mucositis, and esophagitis, leading some investigators to mandate placement of enteral feeding tubes before treatment initiation.

The seminal phase 3 United States Radiation Therapy Oncology Group (RTOG) trial 85-01 demonstrated the superiority of chemoradiotherapy over radiation alone[36]. This nonoperative study compared standard-fractionation radiation (64 Gy) with radiation (50 Gy) plus concurrent cisplatin/5-FU. The trial was stopped when data from 121 patients showed an improved median OS in favor of chemoradiotherapy (12.5months versus 8.9 months). Two-year survival was also improved in the chemoradiotherapy group (38% versus 10%), as was 5-year survival (21% versus 0%)[37]. Although most patients treated on this trial had SCC, long-term survival also was seen in the small number of adenocarcinoma patients on the trial, with 13% of patients alive at 5years.

In addition to a survival benefit, disease recurrence was reduced significantly by the addition of chemotherapy to radiation. At 1 year, recurrent disease was observed in 62% of the group that received radiation versus 44% in the chemoradiotherapy arm. Distant recurrence rates were 38% and 22%, respectively. Based on this study, chemoradiotherapy was established as the

standard of care in the nonsurgical management of locally advanced esophageal SCC.

Building on these results, more intensive treatment strategies have been investigated. In the non-operative RTOG 90-12 chemoradiotherapy study, induction chemotherapy with cisplatin/5-FU followed by chemoradiotherapy with the same regimen did not appear to afford any additional benefit[38]. The RTOG 94-05 study compared a total radiation dose of 64.8 Gy versus 50.4 Gy during concurrent cisplatin/5-FU and also failed to demonstrate superior results with the more intense regimen[39]. This study confirmed 50.4 Gy as the standard radiation dose when given in combined therapy with cisplatin/5-FU. Finally, the phase 1/2 RTOG 92-07 trial, which attempted to boost radiation with brachytherapy following external beam radiation, revealed significant toxicity, including a 12% incidence of treatment-related fistulas[40].

Five contemporary randomized trials have compared preoperative chemoradiotherapy followed by surgery versus surgery alone. The results are summarized in the **Table 1**.

Table 1. Results of Preoperative chemoradiotherapy trials in esophageal cancer								
Treatment	**Histology**	**No.**	**R0 Resec'n rate**	**pCR**	**Median Survival**	**Overall Survival**	**Local Failure**	**Ref.**
Pre-op CRT	SqCC (24%) + AdenoCa	50	45%	28%	16.9mo	3y 30%	19%	Urba et al[41]
Surgery	(76%)	50	45%	N/A	17.6mo	3y 16%	42%	
Pre-op CRT	AdenoCa	58	NS	25%	16mo	3y 32%	NS	Walsh et al[42]
Surgery		55		N/A	11mo	3y 6%		
Pre-op CRT	SqCC	143	81%	26%	18.6mo	5y 26%	NS	Bosset et al[43]
Surgery		139	69%	N/A	18.6mo	5y 26%		
Pre-op CRT	SqCC(35%) + AdenoCa	128	80%	16%	22.2mo	NS	15%	Burmeister et al[44]
Surgery	(63%)+ other	128	59%	N/A	19.3mo	NS	26%	
Pre-op CRT	SqCC(25%) + AdenoCa	30	NS	40%	4.5yrs	5y 39%	NS	Tepper et al[45]
Surgery	(75%)	26		NA	1.8yrs	5y 16%	NS	

D. DEFINITIVE CHEMORADIOTHERAPY IN COMPARISON TO NEOADJUVANT CHEMORADIOTHERAPY FOLLOWED BY SURGERY.

Two recent randomized trials have compared definitive chemoradiotherapy versus chemoradiotherapy followed by surgery. The first study was performed by the German Esophageal Cancer Study Group, which assigned 172 patients who had SCC to preoperative therapy (three cycles of cisplatin/5-FU/leucovorin/etoposide, then cisplatin/etoposide and concurrent radiation to 40 Gy) followed by surgery or to the preoperative therapy alone with

a higher radiation dose (to at least 65 Gy) in lieu of surgery[34]. Although local PFS was improved with the addition of surgery (HR for chemoradiotherapy-only group versus surgery group 2.1, 95% CI, 1.3 to 3.5, P=.003), there was only a non-significant trend toward improvement in 3-year OS (31.3% versus 24.4%). Treatment-related mortality was also significantly higher in the surgery group compared with the chemoradiotherapy-only group (12.8% versus 3.5%). Ten-year survival data for this trial recently was presented in abstract form, reaffirming the absence of a significant difference between both groups[47].

The second study is the French FFCD 9102 trial, where 444 eligible patients who had mostly SCC histology underwent initial chemoradiotherapy with cisplatin/ 5-FU[48]. Those who responded to initial therapy then were randomized either to undergo surgery or to receive an additional three cycles of cisplatin/5-FU with radiation, as the authors felt that it would be inappropriate to continue chemoradiotherapy in patients not responding to therapy. Of the 444 patients, 259 were randomized. The 2-year survival rate was not significantly different between both groups (34% in surgery group versus 40% in chemoradiotherapy-only group, P=.44). Locoregional recurrence, however, was higher in the chemoradiotherapy-only group (43% versus 34%), and there was also a higher incidence of stent placement in this group (32% versus 5%). Three-month mortality was significantly higher in the surgery group (9.3% versus 0.8%). Based on these data, the authors concluded that patients who have tumors,

especially of SCC histology, that respond to initial chemoradiotherapy did not derive any survival benefit from subsequent surgery. Patients who underwent surgery did have improved local control of their disease, albeit at the cost of increased treatment-related mortality.

An interesting question that arises from this study is whether patients who do not respond to initial therapy benefit from subsequent surgery. In a recent abstract, the authors discussed the outcome of the 192 of the 451 registered patients from the previous study who were not randomized to further protocol therapy after initial chemotherapy primarily because of a lack of response but also because of medical contraindication or patient refusal[49]. Of these nonrandomized patients, 112 subsequently underwent surgery, with 80 undergoing R0 resections. The median OS for the patients who underwent surgery was significantly superior to the median OS of those who did not (17.3 versus 6.1 months) and was comparable to the median OS of the patients who were randomized. Although there are clear limitations and potential strong confounders to such an analysis, these data may suggest that salvage esophagectomy can be beneficial for a subset of patients who do not respond to initial therapy.

As a related issue, definitive chemoradiotherapy alone versus surgery alone also recently was compared in a Scandinavian phase 3 trial of 91 patients with adenocarcinoma and SCC who were randomized to receive either cisplatin/5-FU and radiation alone or surgery[50]. At a median follow-up of 51.8

months, there was no survival difference between both groups. Although this study may be underpowered to detect small survival differences, the data collectively support definitive chemoradiotherapy as an acceptable approach for patients who have contraindications to surgery.

CHEMOTHERAPY IN METASTATIC ESOPHAGEAL CARCINOMA

A variety of single agents and combination regimens have been evaluated in patients with recurrent or metastatic carcinoma of the esophagus. These patients often have a high tumor burden and poor performance status with little prospect for prolongation of survival. Phase II clinical trials in this population have identified drugs with activity that have been integrated into combined modality regimens for the treatment of earlier-stage disease.

A. Single-Agent Chemotherapy

Studies of single-agent chemotherapy for esophageal cancer are summarized here. Response data for many of the older drugs have come from broad phase I and II trials conducted in the early 1970s, which included small numbers of esophageal cancer patients[51-60]. Bleomycin, 5-FU, mitomycin, and cisplatin have been used most frequently because of their single-agent activity and additive or synergistic effects with radiation. Because of the potential for

pulmonary toxicity, bleomycin is no longer included in combination regimens, having been replaced by 5-FU. Similarly, mitomycin is used less often because of its toxicity profile, which includes hemolytic-uremic syndrome and cumulative myelosuppression.

Seven trials examined the use of cisplatin for single-agent therapy in esophageal cancer patients[58,61-66], six of which used dosages ranging from 50 to 120 mg/m^2 every 3 to 4 weeks. The cumulative response rate in patients with metastatic or recurrent disease was 21%[58,61-66]. Administration of the drug as a single-bolus dose once every 3 weeks and in a divided dose during 5 days every 3 weeks appeared to be equally efficacious. Using a more dose-intense schedule of cisplatin (120 mg/m^2 on day 1 and 15), Miller et al[64]. observed a 73% response rate in 15 patients before surgery.

A randomized phase II trial of cisplatin alone and cisplatin in combination with 5-FU in 92 patients with metastatic squamous cell carcinoma of the esophagus was reported by the EORTC[62]. A 19% response rate was observed in 45 patients receiving single-agent cisplatin (100 mg/m^2 every 3 weeks). The response rate in the combination therapy arm was 35%. No studies of single-agent cisplatin have been performed in patients with adenocarcinoma of the esophagus.

Vinorelbine is a semisynthetic vinca alkaloid that has less neurotoxicity than vincristine and vinblastine. Phase II trials in metastatic

squamous cell cancer of the esophagus report response rates of 20% to 25% using weekly or biweekly dosing schedules[67,68].

Three trials of single-agent paclitaxel have been reported. One used the maximum tolerable dose of 250 mg/m^2, derived from initial phase I trials using a 24-hour infusion schedule[69]. The overall response rate was 32% (34% in 33 patients with adenocarcinoma, and 28% in 18 patients with squamous cell carcinoma). All patients had good performance status, were chemotherapy-naive, and had distant metastases. The second trial tested a regimen of 140 mg/m^2 infused during 96 hours in patients previously treated using a shorter infusion schedule of paclitaxel containing combination chemotherapy[77]. No responses were observed. The third trial evaluated single-agent paclitaxel administered by a weekly 1-hour infusion at a dose of 80 mg/m^2 in a large multicenter phase II setting[71]. A modest response rate of 15% was observed in 65 patients without prior chemotherapy treatment (16% in the 50 patients treated with adenocarcinoma and 13% in the 15 patients treated with squamous cell carcinoma).

Drugs that have been adequately tested in squamous cell cancer of the esophagus and have response rates of less than 5% are trimetrexate, etoposide, ifosamide, and carboplatin. Therefore, substitution of single-agent carboplatin for cisplatin is not recommended when treating patients with either adenocarcinomas or squamous cell carcinomas of the esophagus

B. Combined-Agent Chemotherapy

Older trials (before the mid-1990s) and those in Europe were almost exclusively limited to patients with squamous cell carcinoma. Because esophageal cancer is a relatively uncommon malignancy, many studies include a heterogeneous population of treatment-naive patients with locally advanced intrathoracic disease as well as patients with recurrent or metastatic disease. Not only is there variation in the patient population, but more recent trials usually limit eligibility to patients with no prior chemotherapy and performance status of 0 or 1. Thus, in the absence of comparative trials, newer regimens may appear more effective.

The results for platinum-based combination chemotherapy regimens are detailed in **Table 2**[72,73,62,74,75-93]. Most series consist of small numbers of patients; therefore, the 95% confidence intervals are large and nearly all responses are partial. On average, duration of response ranges from 3 to 6 months. No specific regimen has yet emerged as more efficacious and less toxic than cisplatin and 5-FU.

Table 2. Selected Combination Chemotherapy Regimens for Recurrent and Metastatic Carcinoma of the Esophagus				
Regimen	***Evaluable Patients (n)***	***Histologic Type***	***% CR + PR***	***References***
Cisplatin + bleomycin	17	S	17	*72*
Cisplatin + bleomycin + vindesine	51	S	31	*76*
Cisplatin + bleomycin + Methotrexate	40	S	30	*77,78*
Cisplatin + mitoguazone + vindesine	20	S	40	*79*
Cisplatin + mitoguazone + vinblastine	36	S	11	*80*
Cisplatin + 5-FU	82	S	35	*62*
Oxaliplatin + 5-FU	34	A/S	40	*88*
Carboplatin + vinblastine	16	S	0	*81*
Cisplatin + vinorelbine	71	S	34	*74*
13-*cis*-retinoic acid + interferon-2alpha	15	S/A	0	*84*
5-FU + interferon	57	S/A	26	*82,95*
Cisplatin + 5-FU + interferon	66	S/A	53 (62% S, 32% A)	*83,96*
Cisplatin + etoposide	65	S	48	*85*
	27	A	48	*92*
Cisplatin + etoposide + 5-FU + leucovorin	69	S	34	*97*

CR, complete response; PR, partial response; S, squamous cell carcinoma; 5-FU, 5-fluorouracil; A, adenocarcinoma of esophagus, gastroesophageal junction, cardia; G, gastric cancer

Regimen	*Evaluable Patients (n)*	*Histologic Type*	*% CR + PR*	*References*
Paclitaxel (24 h) + cisplatin every 3 wk	32	S/A	44 (25% S, 46% A)	*100*
Paclitaxel (3 h) + cisplatin every 2 wk	51	S/A	43	*98*
Paclitaxel (3 h) + cisplatin every wk Ã— 6	24	A	50	*99*
Paclitaxel (3 h) + cisplatin + 5-FU every 4 wk	60	S/A	48 (56% S, 46% A)	*101*
Paclitaxel (1 h) + carboplatin every week	37	S/A	54%	*93*
Irinotecan + cisplatin every wk Ã— 4, every 6 wk	35	S/A	57 (66% S, 52% A)	*102*
Irinotecan + cisplatin every wk Ã— 4, every 6 wk	25	A	51	*103*
Docetaxel + irinotecan every wk Ã— 3, every 4 wk	24	S/A	13	*105*
Docetaxel + irinotecan every 3 wk	46	A	26	*104*
Mitomycin + cisplatin + 5-FU Vs. Epirubicin + cisplatin + 5-FU	285 Vs. 289	A/G Vs. A/G	46% A, 38% G Vs. 44% A, 36% G	*94*
CR, complete response; PR, partial response; S, squamous cell carcinoma; 5-FU, 5-fluorouracil; A, adenocarcinoma of esophagus, gastroesophageal junction, cardia; G, gastric cancer				

Dose intensified Cisplatin based chemotherapy:

Cisplatin is one of the most active chemotherapeutic agents in epithelial cancers, especially esophageal cancers. The analysis of dose-intensity (dose delivered per unit time) is considered the most appropriate method of analyzing dose-response relationships[106].

To standardize terminology, dose-intensity is usually expressed as milligrams per square meter per week, regardless of the actual schedule of administration. Conventional chemotherapy regimens in esophageal cancer using Cisplatin achieve a dose intensity ranging from 15mg/m^2/week to about 35mg/m^2/week.

Rationale of the Proposed Study:

This pilot study builds on the data that Cisplatin based chemotherapy is the standard of chemotherapeutic management of esophageal carcinomas, both in the adjuvant and metastatic scenarios. By the proposed dosing of induction chemotherapy using Cisplatin and 5-Fluorouracil, the following objectives are being tested;

1. A Greater dose intensity is achieved by increasing the dose to 200mg/m^2 delivered over 5weeks, which in the conventional treatment is delivered over 6-8weeks.

Dose intensity achieved is equivalent to 40mg/m^2/week. In common conventional chemotherapy regimens, the dose intensity achieved is in the range of 15-35 mg/m^2/week.

2. A greater dose intensity will improve the response rates to treatment

3. A higher dose intensity also decreases the chances of accelerated repopulation by resistant and less responsive clones of malignant cells, which will reduce recurrence rates and thus, has the ability to improve survival.

4. An improved response rate will help achieve an earlier and possibly more sustained dysphagia relief to the patient, and tumor down staging to the treating physician.

5. By using cheaper and readily available conventional chemotherapeutic drugs and optimizing the dose intensity there after, an affordable and new standard of care in chemotherapeutic management of esophageal cancer is envisaged.

Possible drawbacks of this treatment regimen

1. Inpatient treatment

2. Longer hospital stay

3. Higher incidence of toxicity of therapy, especially Cisplatin related toxicity viz. Emesis, Nephrotoxicity, Neurotoxicity and Ototoxicity. This can be circumvented by fractionating the dose into 10 equal doses given over 10days and improving the hydration and supportive care along with careful and close monitoring of the patient.

AIM OF THE STUDY

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*This trial is designed to determine if the treatment arm under consideration is promising enough to be pursued in a phase II study***.**

- **To determine the feasibility of treatment delivery, patient tolerance, and acute toxicities**
- **To describe the response (including dysphagia relief) on completion of the test chemotherapy schedule.**

SUBJECTS AND METHODS

SUBJECTS AND METHODS

PATIENT SELECTION

(Note: As per NCI (National Cancer Institute), USA guidelines, exceptions to eligibility are not permitted)

1 Conditions for Patient Eligibility

1.1 Pathologically (histologic or cytologic) proven diagnosis of primary squamous cell or adenocarcinoma of the esophagus or esophageal-gastric junction within 12 weeks prior to registration

1.1.1 Patients with celiac, perigastric, mediastinal or supraclavicular adenopathy are eligible.

1.1.2 Patients with cervical esophageal carcinoma are eligible

1.1.3 Patients with non-regional adenopathy and distant metastasis are eligible

1.2 Stage T1N1M0; T2-4, Any N, M0; Any T, Any N, M1a, M1b based upon the following minimum diagnostic work-up:

1.2.1 History/physical examination within 6 weeks prior to registration

1.2.2 Chest/Whole Abdominal CT within 6 weeks prior to registration

1.2.3 ECG within 6 weeks of study entry

1.2.4 Endoscopy with biopsy or cytology by fine needle aspiration (FNA) (must be able to document histologic subtype) within 12 weeks of study entry. Patients with T3-4 proximal thoracic esophageal tumors (15-25 cm) must undergo bronchoscopy to check for fistula.

(NOTE: Any images from endoscopic procedures up to the time of progression must be kept in the patient's confidential study file.)

1.3 Zubrod/ECOG performance status 0-2

1.4 Age ≥ 18

1.5 CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows:

1.5.1 Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3

1.5.2 Platelets ≥ 100,000 cells/mm3

1.5.3 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

1.6 Additional laboratory studies obtained within 2 weeks prior to registration on study

1.6.1 Creatinine ≤ 1.5 mg/dl

1.6.2 Bilirubin ≤ 1.5 x upper limit of normal

1.6.3 AST ≤ 3 x upper limit of normal

1.6.4 Serum pregnancy test for women of childbearing potential

1.7 Patient's total intake (oral/enteral) must be ≥ 1500 kCal/day

1.8 Patient must provide study-specific informed consent prior to study entry

1.9 Women of childbearing potential and male participants must practice adequate contraception

2 Conditions for Patient Ineligibility

2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 2 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible).

2.2 Prior systemic chemotherapy for esophageal cancer; note that prior chemotherapy for a different cancer is allowable. See Section 2.1.

2.3 Prior radiation therapy that would result in overlap of planned radiation therapy fields.

2.4 Prior platinum-based therapy.

2.5 Prior allergic reaction to the study drugs involved in this protocol.

2.6 Severe, active comorbidity, defined as follows:

2.6.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 3 months

2.6.2 Transmural myocardial infarction within the last 6 months

2.6.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

2.6.4 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study

therapy at the time of registration

2.6.5 Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients.

2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

2.8 Women who are nursing.

PRETREATMENT EVALUATIONS

Required Evaluations

1. Complete history and exam including weight with an assessment of the patient's performance status;

2. All patients must be evaluated by a Medical Oncologist prior to study entry.

3. Laboratory Studies (within 2 weeks prior to treatment)

- CBC

- Serum creatinine, electrolytes, SGOT, AST, LDH, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, inorganic phosphorous, calcium, BUN, magnesium).
- Calculated creatinine clearance (optional)

A venous access(an IV line, a long line, subclavian catheter, or implantable device) will be established in all patients.

4. Imaging Studies(within 4 weeks prior to randomization)

- CT Scan of the Chest and Abdomen (MRIs are acceptable)
- Upper GI endoscopy (Endoscopic ultrasonography and double contrast upper GI radiographs are highly recommended but not required.)
- Chest X-ray
- Data on T stage, N stage will be collected.
- Whenever possible, EUS/FNA of the nodes is highly desirable to improve accuracy.

5. Bronchoscopy is required if the lesion is < 30 cm from the incisors to exclude TE fistula or invasion.

6. Biopsy of supraclavicular node if clinically or radiographically enlarged;

7. Lymph node biopsy is not mandatory. Nodes < 1 cm need not be biopsied. For nodes 1-2 cm, a biopsy should definitely be considered.

8. ECG; bone scan (if alkaline phosphatase is elevated ≥ 1 .5 x normal);

9. Nutritional Assessment

Patients should ingest either more than 1.5 x their Basal Energy Expenditure (BEE) as measured by the Harris-Benedict equation or more than 1,000 calories per square meter of body surface area (1700 calories for the average 1.7 meter individual). If the patient is not able to ingest this amount by mouth, a gastrostomy or jejunostomy tube to accomplish this is required. Intravenous hyperalimentation is discouraged. The nutritional supplements should amount to a minimum 1.75 x the BEE or 1200 calories per square of body surface area but no more than 2.25 x the BEE or 1600 calories per meter square of body surface area unless the patient can be shown to be hypometabolic.

Patients should be instructed about food intake during treatment. Instructions should include recommending the avoidance of irritants (including alcohol, citrus/acidic foods, sharp foods, or foods with extreme temperatures). Documentation of any nutritional intervention, including oral high- protein nutritional supplements, feeding tubes, and parenteral or enteral nutrition is required.

10. Harris-Benedict Equation to Measure BEE

Men

66.4730 + (13.7516 x wt in kg) + (5.0033 x ht in cm) - (6.75 x age)

Women

655.0955 + (9.5634 x wt in kg) + (1.8496 x ht in cm) - (4.6756 x age)

Daily Caloric Requirement = BEE x 1.75

$$\text{Daily Protein Requirement} = \frac{\text{Caloric Requirement} \times 6.25}{150}$$

Optional Evaluation

2.1 Bilateral audiogram (encouraged in patients with clinical hearing loss)

TREATMENT: CHEMOTHERAPY

Protocol treatment must begin within 10 business days after registration.

Induction Chemotherapy

1. Schedule

- Inpatient administration of chemotherapy is mandatory. Patients will need an intravenous line or a double lumen central line placed for chemotherapy administration.
- Chemotherapy schedule will be as follows:

DRUGS	Daily DOSE	Schedule	On DAYS
Cisplatin	20mg/m2	i.v. in 1hour	1-10
5-Fluorouracil	250mg/m2	8hour i.v. infusion	1-10

- Subsequent courses of off-protocol chemotherapy may be decreased by 20% based on toxicity experienced during the test course; however, the *doses of chemotherapy drugs will not be increased*.
- Adequate hydration, electrolyte supplementation, and anti-emetic support will be provided when administering cisplatin. Patients will

receive at least 1.0 liter of 1/2 NS with magnesium and potassium supplements intravenously on all cisplatin days. All patients will be encouraged to drink at least 2L of fluid daily.

The subsequent course of off-protocol treatment will be initiated not earlier than day 36 provided the patient has recovered from all toxicities (grade < 1) except alopecia and provided that peripheral counts (absolute granulocyte count >1,500/μL and platelet count >100,000/μL) are adequate.

2. Further off-protocol therapeutic decision making

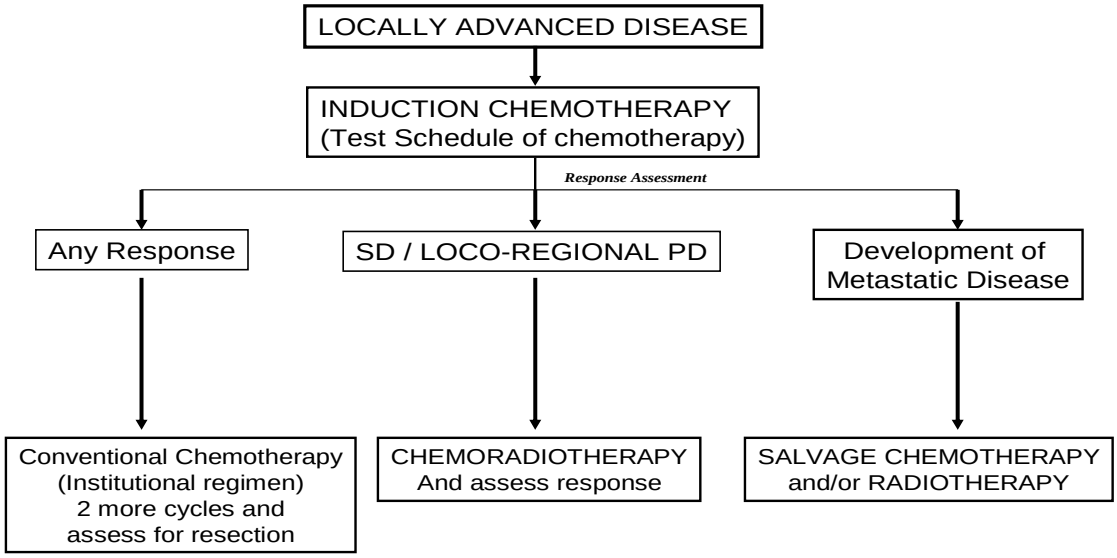
The following decision guidelines will be used for recommending the next step, after patients have received course of chemotherapy on protocol:

a. In case of Localized Disease at the time of registration

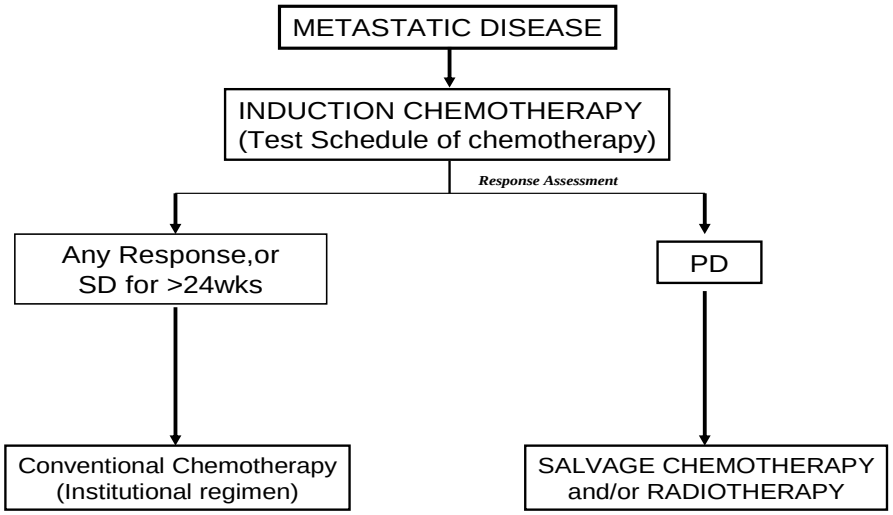
- Local progression after the first cycle of chemotherapy- Proceed to chemoradiotherapy
- Any response to the test course of chemotherapy- Assessment of resectability by the Surgical Gastroenterologist
    a. If resectable-Proceed with surgery
    b. If still unresectable- proceed with Cisplatin based conventional institutional chemotherapy
- Stable disease-Proceed to chemoradiotherapy.
- Development of distant metastases anytime Salvage therapy off protocol

b. In case of Metastatic Disease at the time of registration

- Local progression or development of new sites of metastases - Salvage therapy which may include chemotherapy and/or radiotherapy and/or surgery as required.
- Any response- Proceed with Cisplatin based conventional institutional chemotherapy until progressive disease or 6 cycles whichever is earlier.



SD-Stable Disease, PD-Progressive Disease



SD-Stable Disease, PD-Progressive Disease

3. Dose Modifications for Chemotherapy treatment thereafter

Reduction of chemotherapy dose will be based on the degree of hematologic and non-hematologic toxicities. The goal is not to induce grade 3 nonhematologic toxicity or grade 4 hematologic toxicity.

If the granulocyte level drops below 1000, counts should be performed every other day until the level rises above 1000.

Dose modification cisplatin based on hematologic toxicities

Granulocyte Nadir		Platelet Nadir	Dose Modification
>1,000	AND	>75,000	No Change
> 500 but <1,000	AND/OR	>50,000 but <75,000	No Change
<500 for more than >5 days	AND/OR	<50,000	decrease 20%
Infection or bleeding related to myelosuppression			decrease 20%

The following **dose modifications for 5-FU and cisplatin based on non-hematologic toxicities** will be applicable to all subsequent courses.

Toxicity Grade	Dose Modification
0-2	No Change
3* or 4	Decrease 20%

*Does not apply to alopecia or grade 3 nausea and vomiting

Dose modification for cisplatin based upon renal insufficiency will be as follows:

Serum Creatinine*(mg/dL)	Daily Dose
< 1.4	No change
> 1.4 but < 2.0	Decrease 50%
> 2.0	Discontinue

*In a well-hydrated state (2 readings necessary when abnormal)

Anaphylaxis (Cisplatin)

Severe allergic reactions to cisplatin are not uncommon. Patients who exhibit anaphylactic-type allergic reactions should not receive further cisplatin.

Nonhematologic Toxicity

The following toxicities are anticipated: nausea, vomiting, diarrhea, mucositis, phlebitis, fatigue, anorexia, myelosuppression, thrombocytopenia, renal dysfunction, ototoxicity, peripheral neuropathy, and dry skin.

This study will utilize the CTC version 3.0 for toxicity and Adverse Event reporting. A copy of the CTC version can be downloaded from the CTEP home page (http://ctep.info.nih.gov). The dose levels of cisplatin are outlined in the following table:

Dose levels	cisplatin mg/m2
Starting	20
20% decrease	16

Dose Modification of Cisplatin

Dose reductions for neurotoxicity, mucositis, fatigue (grade 4 only), oto-, and renal toxicity are outlined in the following table:

Neurotoxicity/ Fatigue*/ Mucositis	Ototox.	Creatinine Clearance		Creatinine	Dose Level, Cisplatin
		≥ 60 ml/min	Or	≤ 1.5	Starting dose- 20 mg/m2
		50≤ clearance< 60	Or	1.5 < creatinine <2	Decrease 20% to 16 mg/m2
		< 50 ml/min	Or	≥ 2	Hold cisplatin
Initial Grade 3-4					Decrease 20% to 16 mg/m2
	Severe	Any		Any	Hold Cisplatin

*Modification for grade 4 fatigue only and of > 5 days duration.

Dose reductions for cisplatin will be made on the basis of the serum creatinine on the day of treatment, or on the development of grade 3-4 neurologic or ototoxicity, fatigue (grade 4 only and of ≥ 5 days duration), mucositis, diarrhea (grade 4 only), or nausea/vomiting/dehydration (grade 4 only). A creatinine clearance (optional) may be obtained to evaluate a rise in serum creatinine and may also be used to adjust the cisplatin dose. However, a creatinine clearance is not mandatory. If the serum creatinine on the day of treatment is > 1.5 mg/dl but < 2.0 mg/dl, and the serum creatinine is used to adjust the dose, the patient should be euvolemic and the value must be confirmed by a second serum creatinine. Modification for grade 4 diarrhea or grade 4 nausea/vomiting/ dehydration (hospitalization required) will be made for cisplatin only; no modification of paclitaxel will be made for these toxicities.

With the 1st cycle of chemotherapy, reduction of cisplatin will not be based on nausea, vomiting, diarrhea, or dehydration but on stated level of neurotoxicity or mucositis (grade 3-4) or fatigue (grade 4 only).

With the subsequent cycle of chemotherapy, dose modifications will be based on other grade 3-4 toxicities, including nausea, vomiting, dehydration, or diarrhea.

Toxicity Grade (Nausea/Vomiting/Diarrhea/Dehydration)	Cisplatin Dose Modification
0-3	No Change
Initial Grade 4 (Hospitalization)	Decrease 20%

If more than one grade 3-4 nonhematologic toxicity attributable to cisplatin occurs during the 1st cycle, then a single dose modification of cisplatin for the greatest toxicity observed will be made for the 2nd cycle

Dose Modification During FU Chemotherapy

Potential toxicities of chemoradiotherapy include nausea, loss of appetite, vomiting, malaise, mucositis, hand-foot syndrome, and rarely myelosuppression and neuropathy. Major toxicities include mucositis, hand-foot syndrome, and rarely diarrhea. Patients will be observed weekly.

5-FU doses will be modified as follows based on the level of toxic effects observed during chemotherapy:

Toxicity Grade	Dose Modification
0-2	No change
3 or 4*	Hold 5-FU for 5 days and resume, provided the toxicity has substantially resolved or grade <1.

*Does not apply to alopecia or grade 3 nausea and vomiting

3. Agents

A. Cisplatin (CDPP)

Formulation

Cisplatin is available as a 1 mg/ml solution in 10, 50 and 100 mg vials.

Pharmacology

The dominant mode of action of cisplatin appears to involve the formation of a bifunctional adduct resulting in DNA crosslinks. How this kills the cell remains unclear. There are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 18 to 37 minutes, and a secondary phase ranging from 44 to 190 hours. This prolonged phase is due to protein binding which exceeds 90%. Urinary excretion is incomplete with only 27 to 45% excreted in the first five days. The initial fractions are largely unchanged drugs.

Supplier

Cisplatin is available commercially and supplied by the Government drug store

Storage

The intact vials should be stored at room temperature. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride containing vehicle such as D5NS, NS, or D5-1/2NS (ppt. occurs in D5W). Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes. Cisplatin should be given immediately after preparation as a slow intravenous infusion.

Side Effects and Toxicities

Includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), hyperuricemia, seizures, rash, ocular toxicities, rare cardiac abnormalities, or possible acute myeloid leukemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppresion, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Rare complications are loss of taste, allergic reactions, and loss of muscle or nerve function.

B. Fluorouracil (5-FU)

Formulation

5-FU is available in 5-ml ampules, as a colorless to faint yellow aqueous solution containing 250 mg 5-FU, with pH adjusted to approximately 9.0 with sodium hydroxide. Administration of 5-FU should be only by the intravenous route taking care to avoid extravasation.

Pharmacology

5-FU is a marketed drug available in 500 mg vials. It is fluorinated pyrimidine belonging to the category of antimetabolites. 5-FU resembles the natural uracil molecule in structure, except that a hydrogen atom has been replaced by a fluorine atom in the 5 position.

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to the thymidylic acid. In this fashion 5-FU interferes with the synthesis of DNA and to a lesser extent inhibits the formation of ribonucleic division and growth; the effect of fluorouracil may be to create a thymidine deficiency which provides unbalanced growth and death of the cell.

Supplier

5-FU is available commercially and supplied by the Government drug store.

Storage

Although 5-FU solution may discolor slightly during storage, the potency and safety are not adversely affected. Store at room temperature (49°-86°F). Protect

from light. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to l40°F with vigorous shaking; allow to cool to body temperature before using.

Side Effects and Toxicities

The spectrum of toxicity includes stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea with cramping and/or bleeding, anorexia, nausea and emesis are commonly seen during therapy. Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and l4th days after the first dose, although uncommonly, the maximal depression may be delayed for as long as 20 days.

By the 30th day the count has usually returned to the normal range. Alopecia and dermatitis may be seen. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. Other side effects include myocardial ischemia, angina, lethargy, malaise, headache, allergic reactions, disorientation, confusion, euphoria, dizziness, uncoordination, visual changes, photosensitivity (eyes and skin), nail changes including loss of nails, skin thickening, cracking, dryness or sloughing, vein pigmentation, biliary sclerosis, or acaculous cholecystitis.

PATIENT ASSESSMENTS

1. **Study Parameters**

Parameter	Prior to Randomization (≤ 28 days)	During the chemo cycle	After the chemo	Week 6 from D-1 of chemotherapy Initiation
History & Physical Exam'n	+	+	+	+
CBC, diff, platelets	+(e)	+(a)	+	+
Blood & Serum Chem (g)	+(e)	+(a)	+	+
CXR-PA	+(e)			+
Bronchoscopy (f)	+			+
Barium contrast X-rays	+(c)			+
Chest & Abdominal CT (MRIs acceptable)	+			+
ECG	+			
Endoscopy & USG (Endo-USG not mandatory)	+			+
Bone Scan	+(d)			+(d)
PFTs	+(c)			
Biopsy	+			As needed
Toxicity			+	+

a. must be done thrice in a week during chemotherapy

b. if clinically indicated

c. optional (but highly desirable)

d. if serum alkaline phosphatase elevated ≥ 1.5 times normal

e. within 2 weeks prior to randomization

f. if tumor is < 30 cm from the incisors.

g. serum creatinine, electrolytes, SGOT, AST, LDH, Alk phos, total bilirubin, total protein, albumin, uric acid, phos, calcium, BUN, mg

2. **Criteria for Response**

These tumors are not measurable and thus, response is not the primary endpoint of this study.

The rate of negative endoscopy or regression in tumor bulk at Day 36 would be the equivalent of a complete response or partial response, respectively.

3. **Criteria for Progression of Disease**

- While it is recognized that it is not always possible to obtain pathologic proof of progressive disease, biopsy or autopsy material confirming recurrent cancer is highly desirable and every reasonable attempt to obtain such is encouraged.
- In the absence of histologic or cytologic proof of recurrence, clinical evidence (including new masses on CT scan, new lesions on bone scan, ascites not explained by other causes, or enlarging mass by endoscopic U/S), although highly suspicious of recurrent disease will not result in change in the patient's management. These findings should lead to a search for a mass that could be biopsied.
- Patients who develop progression of disease at the primary site while receiving test chemotherapy schedule or develop metastatic disease will be considered treatment failures. They may be treated with any form of

palliative therapy at the discretion of the treating medical oncologist based on institute policy.

- Patients who develop local recurrence only may be offered surgery; they will be considered treatment failures. Those who develop metastases may be offered chemotherapy. They will be considered treatment failures. The regimen chosen may include a variety of phase II agents under study or conventional chemotherapy.
- The dates and sites of all failure patterns must be reported.

4. **Criteria for Removal From Study Analysis**

Efforts shall be made to account for all patients entered into the study during the evaluation of results. However, in detailed evaluation, the following patient categories will be considered.

- Early Deaths: Those patients who died within six weeks of beginning therapy as a result of an event not related to esophageal cancer or to the study drugs.
- Lost to Follow-up: Those patients in whom there is inadequate information to judge tumor response because of loss of contact in which repeated attempts to obtain information are unsuccessful.
- Major Protocol Violations: Patients who receive further therapy or deviate from the treatment program by either adding a chemotherapeutic agent or by substantially modifying the dosage and schedule of the study drugs.

RESULTS

RESULTS

STUDY POPULATION AND COMPLIANCE TO TREATMENT

Between May 2009 and April 2010, 30 patients met the eligibility criteria of the protocol and were recruited. Three patients were excluded from the study because they opted out of the protocol therapy early on (one patient), did not receive protocol therapy (one patient), or had delinquent data (one patient). The remaining 27 patients are considered in the feasibility, toxicity and response analysis. **Table 3** lists pretreatment patient and tumor characteristics.

The median age was 56years (Range 25years to 67years). Men comprised 78 % of patients. 78% patients were current or former smokers, 55% were alcohol abusers and about 10% of them were tobacco chewers. 89% of patients consumed non-vegetarian food also in their diet. The performance status by ECOG was 1 in 74% and 2 in 26% of patients. By histological subtype, as determined by the pathology department of our institution at the time of registration, 89% were Squamous cell carcinoma and 11% were adenocarcinoma. 2 patients had a history of reflux disease and were diagnosed with adenocarcinomas of the lower third of esophagus. The grade of disease was Grade- III in 45% of patients, Grade-II in 33% and Grade-I in 22% of patients. The sites of disease, as determined by endoscopy and imaging investigations at the time of registration were upper one-third of thoracic esophagus in 15% of patients, middle one third in 55% of patients and lower third of thoracic

esophagus in 30% of patients. None of the patients registered had a primary disease of the cervical esophagus or esophago-gastric junction. 37% patients had metastatic disease at presentation. Common sites of metastasis were non-regional lymph nodes and lung. 15% and 22% patients had tracheo-esophageal fistula and aortic infiltration, respectively.

Dysphagia was the most common and troubling symptom at presentation. Nausea, Vomiting and pain were the other common symptoms complained by the patients. Nasogastric tube feeding was required prior to treatment in 48% of patients.

The chemotherapy regimen was according to protocol specification in all patients (100%). The duration of protocol-administered treatment was 10 days in all the 27 patients (100%). All the patients received both Cisplatin and 5-Fluorouracil as per protocol specification without interruption or deviations. A delay to start subsequent off-protocol conventional therapy was observed in 27% of patients. This was significant in 4 patients who had a delay of 7-14 days, but not unusual. It was related to the toxicity of protocol-administered therapy.

Table 3. Distribution of Patient and Tumor Characteristics		
Variable	**No. of Patients**	**Percentage %***
SEX		
Male	21	78
Female	6	22
AGE (years)		
Median	56 years	
Range	25- 67 years	
ECOG Scale		
1	20	74
2	7	26
HABITS		
Smoking	21	78
Alcohol abuse	15	56
Tobacco Chewing	3	11
HISTORY OF REFLUX DISEASE	2	7
HISTORY OF CAUSTIC INJURY	1	4
DIET		
Mixed	24	89
Vegetarian	3	11
* Percentages have been rounded, not all percentages add up to 100%		

Variable	No. of Patients	%*
COMMON SYMPTOMS		
Dysphagia	27	100
Nausea/Vomiting	12	44
Pain	8	30
Abdominal Pain	2	7
Loss of Appetite & Weight	2	7
Neck Swelling	1	4
FEEDING TUBE PRIOR TO TREATMENT		
YES	13	48
NO	14	52
SITE		
Upper third thoracic	4	15
Middle third Thoracic	15	55
Lower third Thoracic	8	30
PATHOLOGICAL SUBTYPE		
Squamous Cell Carcinoma	24	89
Adenocarcinoma	3	11
GRADE (Squamous Cell Carcinoma)		
Grade- I	6	22
Grade- II	9	33
Grade-III	12	45
AJCC Stage Grouping (2002)		
Stage IIA	5	18
Stage IIB	2	8
Stage III	10	37
Stage IVA	4	15
Stage IVB	6	22

* Percentages have been rounded, not all percentages add up to 100%

ACUTE TOXICITY

Acute toxicities were manageable and did not cause life threatening or crippling consequences. There were no treatment related deaths. 1 patient experienced acute grade-4 toxicity and 4 patients had acute grade-3. The acute grade 4 toxicity observed was hematological toxicity. Grade 3 toxicities observed were hematological toxicity, nausea/vomiting and febrile neutropenia. **Table 4** lists the type and frequency of side-effects.

A delay in starting subsequent therapy was observed in 10 patients. This was 7-14 days in 4 patients and was due to febrile neutropenia. Other patients (6) had a delays ranging from 1-5 days and these were considered acceptable. Creatinine Clearance was measured pre-treatment and week 5 post-treatment (**Table 5**). There was a ≤10ml/min drop in 18patients. In 9 patients, the drop in creatinine clearance was 11-20ml/min. This was probably due to the high dose intensity of Cisplatin. However, only 3 of the latter group of patients had elevation of Serum creatinine ≥ 1.5mg/dl, which normalized over ≤6 days and thus, did not mandate dose modifications in subsequent therapy. Of the 14 patients who did not have any feeding tube placement prior to the start of treatment, 4 patients received feeding tube placement during or after treatment. At the time of response assessment, 23 patient had felt subjective improvement and feeding tube was removed in 13patients.

Table 4 - Type and Frequency of Acute Side effects Observed in 27 patients					
	No. of Patients				
Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemoglobin	9	-	4	-	-
Leucocytes	17	6	3	1	-
Neutrophils	11	6	3	1	-
Platelets	16	2	3	-	-
Infection, Febrile Neutropenia	-	-	4	-	-
Mucositis	10	17	-	-	-
Dehydration	7	5	-	-	-
Nausea/Vomiting	-	23	4	-	-
Auditory	-	-	-	-	-
Liver function	-	-	-	-	-
Renal failure	-	-	-	-	-
Sensory Neuropathy	3	-	-	-	-
Motor Neurpoathy	-	-	-	-	-

Table 5 - Drop in Creatinine Clearance, Week 5				
	1-10 ml/min	11-20 ml/min	21-30 ml/min	>30 ml/min
Drop in Creatinine Clearance	18	9*	-	-
* 3 patients recorded a Serum Creatinine ≥ 1.5 mg/dl, which later normalized.				

TUMOR RESPONSE

Overall response to therapy was 48.1% (13 patients). This included partial responses only, as complete responses were not seen in any of the patients at the time of assessment. 3 (11.1%) patients had progressive disease, and 11 (40.8%) patients had stable disease. Patient reported improvement in symptoms (**dysphagia relief**) was seen in 85.2% of patients. This correlated with the achievement of partial response and/or stable disease in all these patients. Figures 1 to 5 illustrate the response distribution and their correlates.

No progression was seen in 3 patients with Adenocarcinoma of esophagus. Relationship between pathological subtype and the type of response reached a 95% Confidence Interval (CI) of 0.33 (RANGE=0.33-0.5). Carcinomas involving the middle third esophagus did not show progression following the test regimen. The relationship between the site of carcinoma esophagus and type of response had a 95% CI of 1.02 (range: 1-1.5). Clinical benefit of therapy was more in high grade carcinomas than low or intermediate grade. The high grade tumors did not show progression after therapy, whereas 2 patients with low-grade and 1 patient with intermediate grade cancer showed progressive disease (95% CI= 1, range= 0.667-1). The response rate was 52.9% in patients with loco-regional disease and 40% in patients with metastatic (Stage IV) disease. Responses were observed in all sites of disease including 13 of 27 esophageal

lesions, 5 out of 11 patients with nodal metastasis and 4 out of 10 patients with metastatic disease. All the 4 patients with tracheo-esophageal fistula showed partial response, and there was closure of fistula in 2 patients. Among the 6 patients with aortic infiltration, 3 showed partial response. Progression was seen in 3 of the 27 esophageal lesions, 2 out of 11 nodal sites and 3 out of 10 patients with metastatic disease.

All 27 patients had dysphagia on study entry, 13 of whom were on Ryle's tube feeding. Of the remaining 14, 9 were swallowing liquids only, 4 swallowing soft food only, and one symptomatic on regular diet. 4 patients received feeding tube placement during treatment. 23 of all 27 patients (85.2%) experienced dysphagia relief with dose intense cisplatin, and 5-FU chemotherapy. The median time to dysphagia relief was 24 days (range, 4-33). Ryle's tube feeding was discontinued in 13 patients by 5weeks post-therapy. Of the 23 patients with dysphagia relief, 13 had endoscopic tumor response that was partial. Dysphagia relief was also observed in 11 patients who had no endoscopic response, but whose tumors became either more pliable or converted from obstructing to nodular, allowing easier passage of the endoscope.

Figure.1

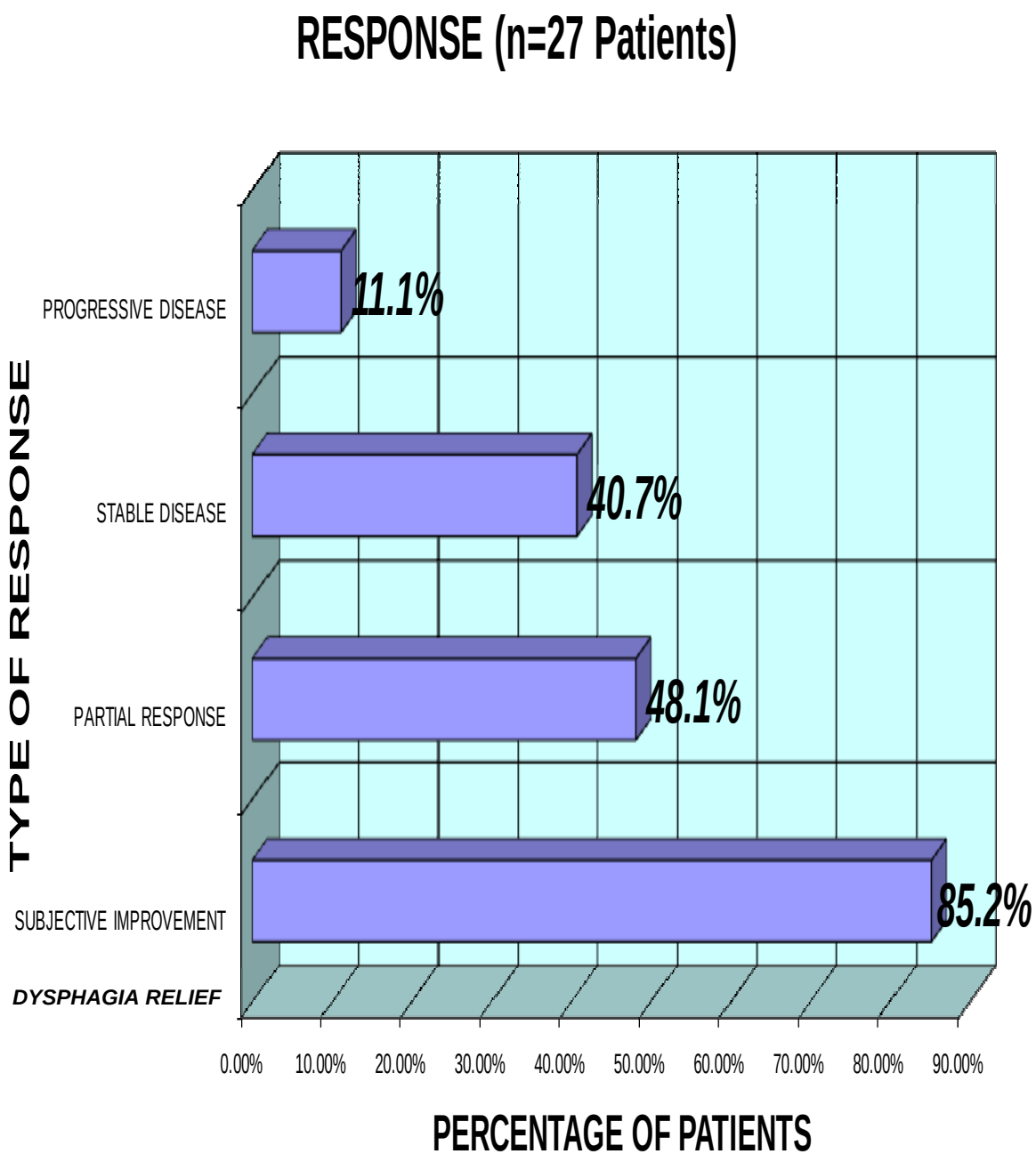

RESPONSE (n=27 Patients)
TYPE OF RESPONSE
PROGRESSIVE DISEASE
STABLE DISEASE
PARTIAL RESPONSE
SUBJECTIVE IMPROVEMENT
DYSPHAGIA RELIEF
11.1%
40.7%
48.1%
85.2%
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%
80.00%
90.00%
PERCENTAGE OF PATIENTS

Figure.2

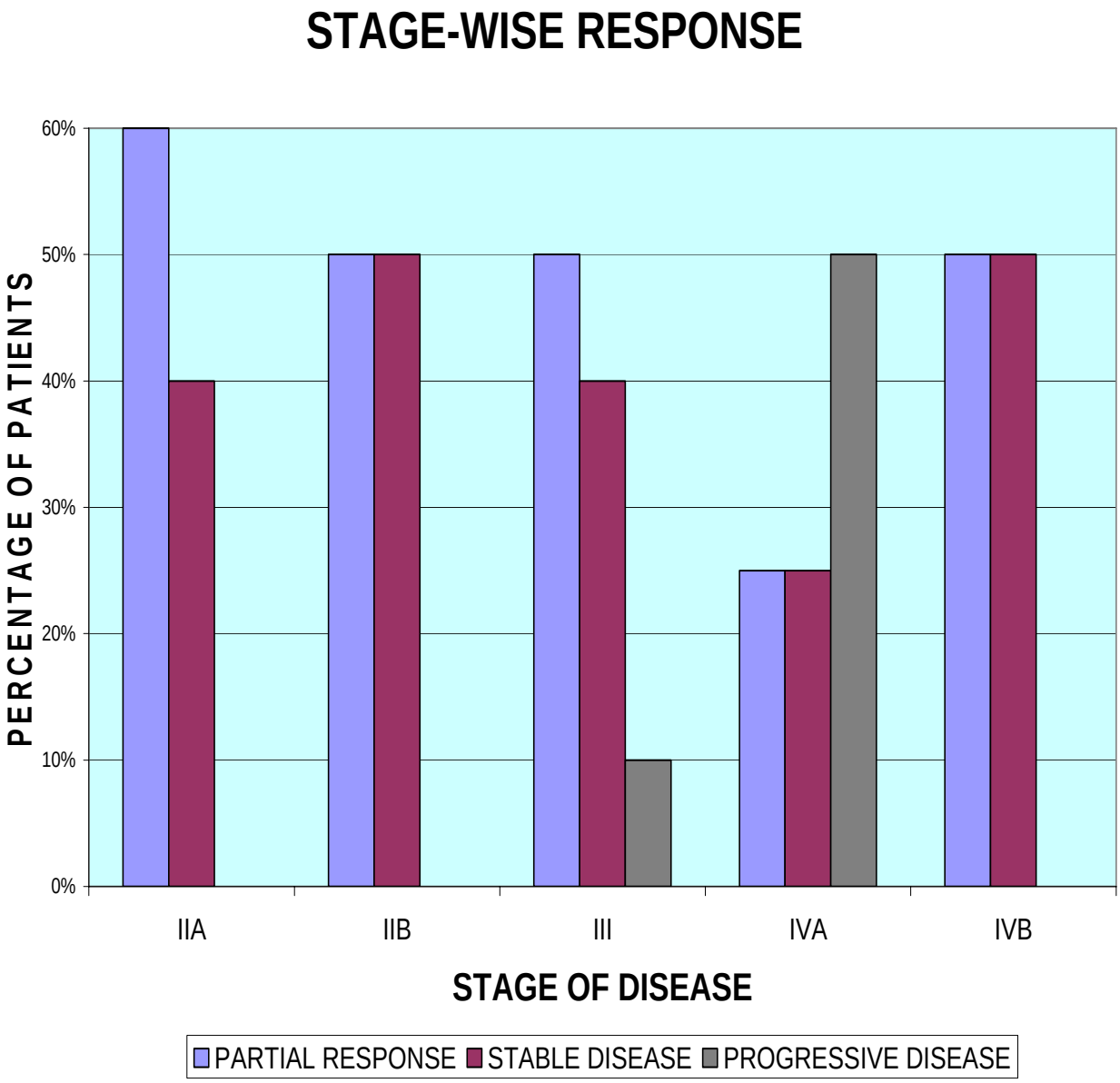

STAGE-WISE RESPONSE
60%
50%
40%
30%
20%
10%
0%
PERCENTAGE OF PATIENTS
IIA
IIB
III
IVA
IVB
STAGE OF DISEASE
PARTIAL RESPONSE
STABLE DISEASE
PROGRESSIVE DISEASE

Figure. 3

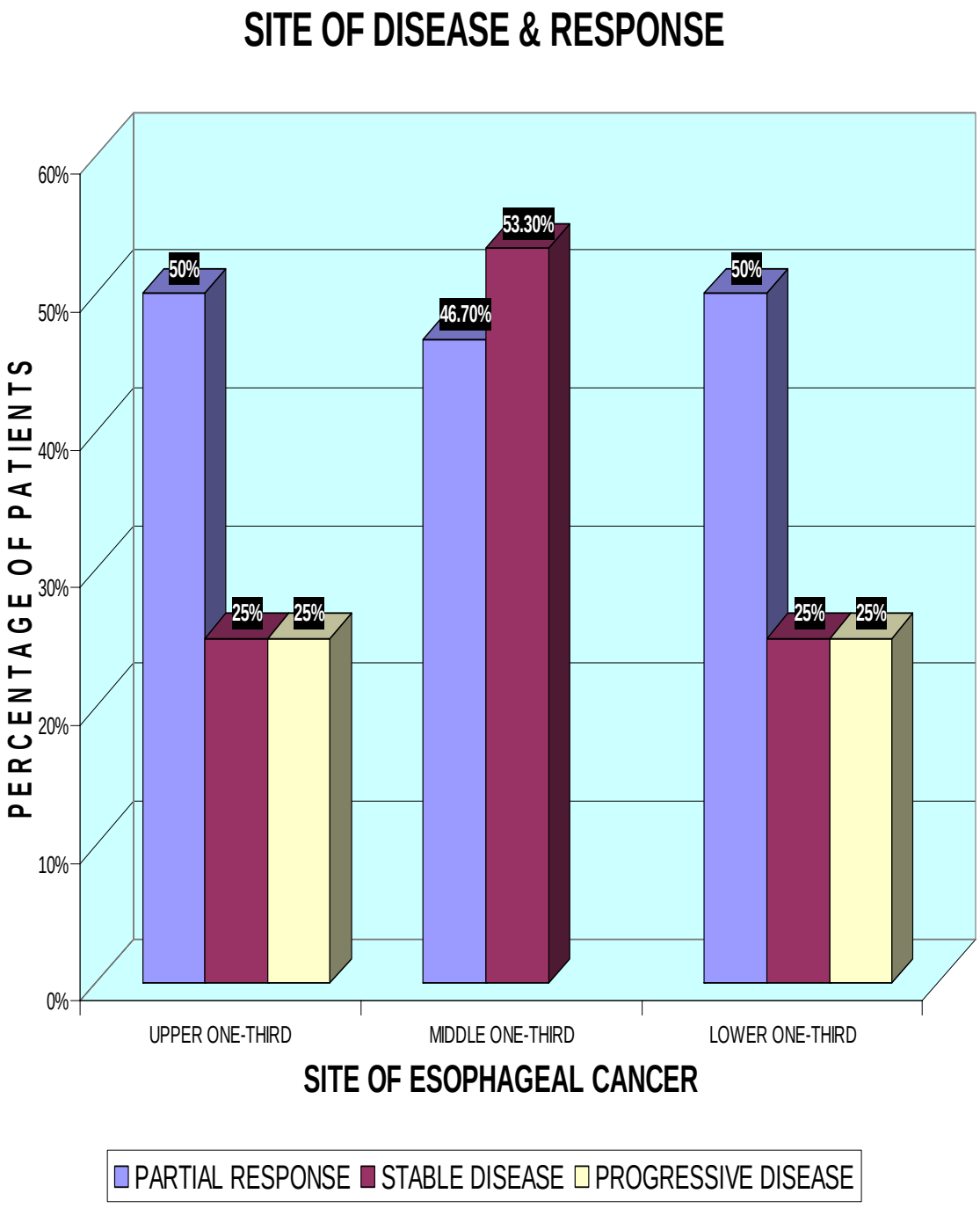

SITE OF DISEASE & RESPONSE
PERCENTAGE OF PATIENTS
60%
50%
40%
30%
20%
10%
0%
50%
25%
25%
46.70%
53.30%
50%
25%
25%
UPPER ONE-THIRD
MIDDLE ONE-THIRD
LOWER ONE-THIRD
SITE OF ESOPHAGEAL CANCER
PARTIAL RESPONSE
STABLE DISEASE
PROGRESSIVE DISEASE

Figure. 4

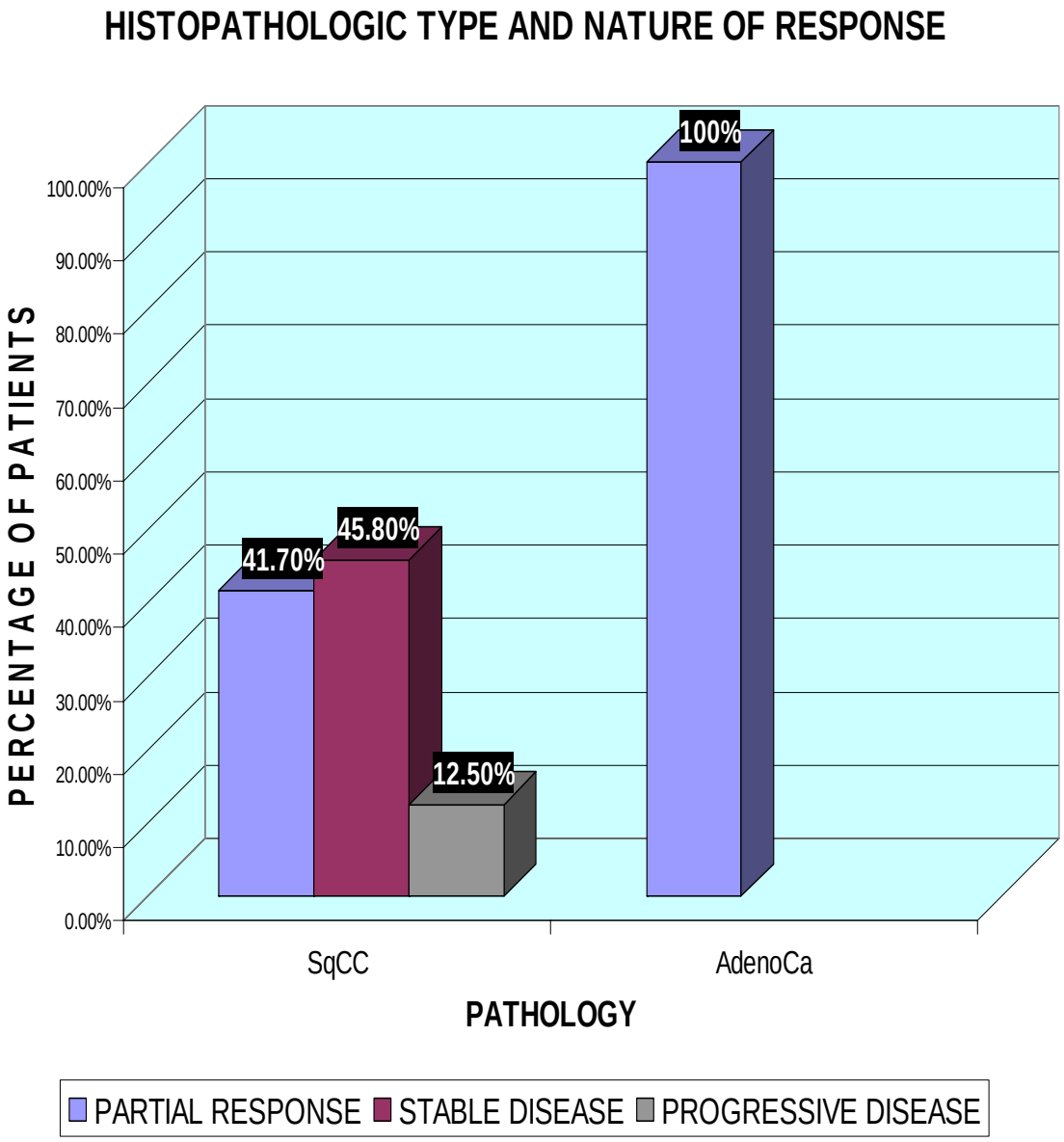
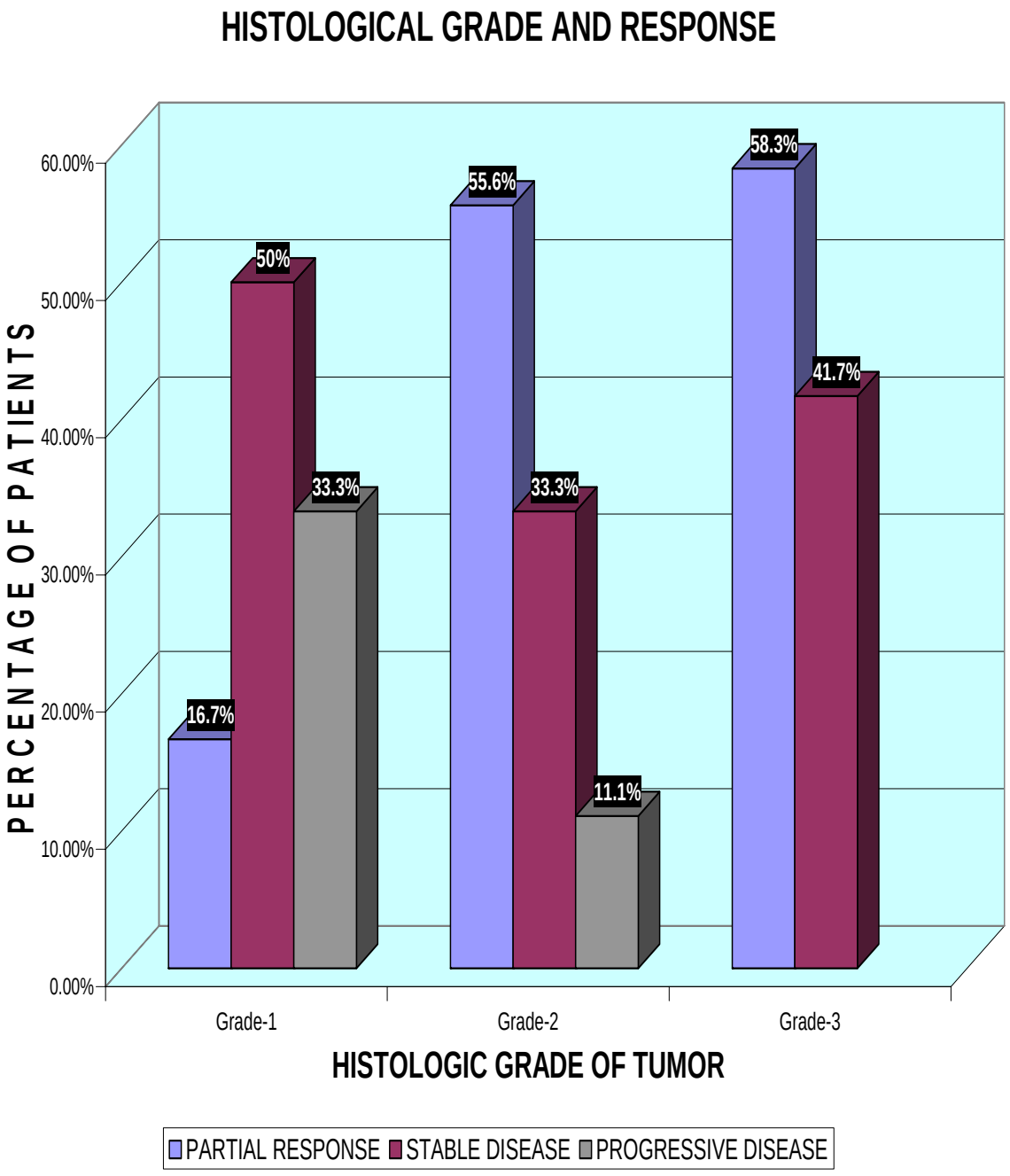

HISTOPATHOLOGIC TYPE AND NATURE OF RESPONSE
PERCENTAGE OF PATIENTS
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
41.70%
45.80%
12.50%
100%
SqCC
AdenoCa
PATHOLOGY
PARTIAL RESPONSE
STABLE DISEASE
PROGRESSIVE DISEASE

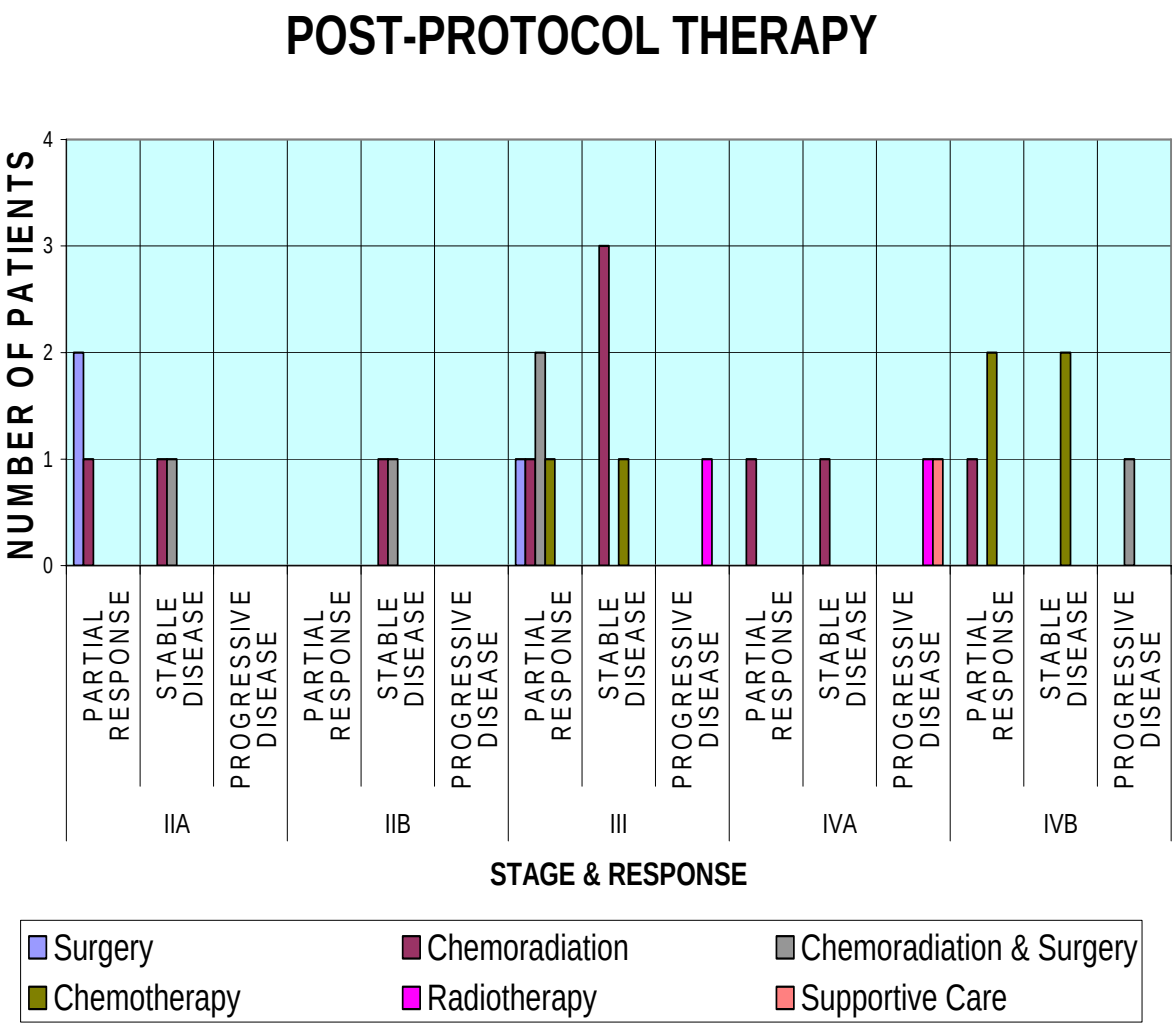
Figure . 5


HISTOLOGICAL GRADE AND RESPONSE
PERCENTAGE OF PATIENTS
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
16.7%
50%
33.3%
55.6%
33.3%
11.1%
58.3%
41.7%
Grade-1
Grade-2
Grade-3
HISTOLOGIC GRADE OF TUMOR
PARTIAL RESPONSE
STABLE DISEASE
PROGRESSIVE DISEASE

POST-PROTOCOL THERAPY UNDERGONE BY THE PATIENTS

Most of the patients who were partial responders received multimodality treatments including surgery and/or chemoirradiation, while those who progressed received palliative radiotherapy, alternative chemotherapy or supportive care treatments. The details of post-protocol conventional treatments received by all the patients are in Fig. 6.

Figure 6



DISCUSSION

DISCUSSION

Cisplatin today is the backbone of most standard chemotherapeutic options in the management of esophageal carcinomas, both Squamous cell carcinomas and Adenocarcinomas. Most new chemotherapeutic agents have not remarkably improved response rates or survival, and are not affordable in settings with resource constraints. This study was devised to assess if increasing the dose intensity of the most active agent in esophageal carcinomas is feasible, and if it can further improve upon the clinical benefit offered by conventional regimens. There are very few published data on the feasibility of cisplatin dose intensification in esophageal carcinomas. Therefore, this study was designed to evaluate the feasibility, toxicity, and activity of high dose Cisplatin and 5-FU in patients with locally advanced and metastatic esophageal carcinomas.

Our results demonstrate the feasibility of one course of dose intense cisplatin based induction chemotherapy in a carefully selected cohort of this population. The delivered dose intensity of 40mg/m^2/week is comparable to the dose intensities received by esophageal, lung and ovarian cancer patients treated with high dose Cisplatin regimens[107, 108, 109]. The response proportion of 48% compares favorably with the response rates observed in previously mentioned esophageal carcinoma chemotherapy trials. In this small cohort of patients, the proportion of responders appeared to have been under a little influence of pathology (Adenocarcinoma) and location of tumor (middle third).

The question of cisplatin dosing has been addressed in other solid tumors with no demonstrable therapeutic benefit derived from dose escalations over 100 mg/m^2/cycle [108]. The Cisplatin dose in this trial (of one course induction) was effective and tolerated well. How much the subsequent cycles of conventional dosing would affect outcomes and toxicity needs to be evaluated further. Without prophylactic filgastrim, myelosuppression was high and resulted in febrile netropenias in 4 patients. There was no treatment related death. One overbearing point however is that, all the patients were inpatients during the treatment, and 28% required additional hospitalization on suspicion of febrile neutropenia or low WBC counts and evaluation of serum creatinine elevations ≥1.5mg/dl(in 1 out of the 3patients). The cisplatin-induced nausea and emesis were manageable with i.v. hydration and antiemetics. Peripheral sensory neuropathy developed only in 3 patients (Grade-1) and was not problematic as it resolved within a week.

The response rates observed in this study may be related to patient selection factors, to the multiday chemotherapy regimen, or to the high dose intensity of cisplatin. We elected to include patients with evaluable loco regional unresectable disease and those with measurable metastatic disease. Response in loco regional disease was assessed by endoscopy and CECT scan more often than by esophagogram(Barium swallow). Endoscopic response assessment has

the advantage of allowing biopsy confirmation in addition to direct tumor visualization. A complete endoscopic response, with the required negative endoscopic biopsies, however is not equivalent to a complete pathologic response because of sampling errors and the inability to assess extramural residual cancer [110]. Complete endoscopic responses have been previously associated with improved survival in patients treated with chemoradiation[111] and are therefore clinically relevant. 13 patients in our series demonstrated partial responses, while none showed complete response on endoscopic examination after the induction treatment.

Another focus of this study was to examine the ability of chemotherapy to relieve dysphagia in symptomatic patients. In this patient cohort, dose intense cisplatin and fluorouracil chemotherapy produced complete and prompt dysphagia relief in 85% of symptomatic patients, contributing to improved quality of life. Complete dysphagia relief was observed both in patients whose primary esophageal tumors responded endoscopically and in those non-responders whose tumors changed in consistency or appearance. Presumably, the improved patency of the esophageal lumen associated with these tumor changes allowed easier passage of food through the cancerous esophageal segrnent [112]. These results compare favorably to the improvement in dysphagia seen in 71% of patients treated with radiation alone[113] and in 60-88% of patients treated with concurrent chemoradiation[111,114]. The durability of

dysphagia relief due to one course of dose intense cisplatin and fluorouracil chemotherapy is difficult to assess because of the subsequent administration of radiation therapy and/or chemoradiation to patients.

CONCLUSION

CONCLUSIONS

In conclusion, we have identified that

- One course of dose intense cisplatin based chemotherapy preceding the standard treatment is a feasible inpatient induction treatment regimen for patients with locally advanced and metastatic esophageal carcinomas, and has an acceptable toxicity profile.

- One course of dose intense cisplatin based induction chemotherapy is an active regimen in esophageal Squamous cell Carcinomas and Adenocarcinomas. In light of the high rates of dysphagia relief and clinical activity that is comparable to conventional chemotherapy, we believe that this is an effective chemotherapy regimen as an inpatient induction therapy.

- This regimen should be considered in larger phase-II clinical studies evaluating induction therapy for a similar group of patients.

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BIBLIOGRAPHY

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ANNEXURES

TNM CLASSIFICATION OF

PRIMARY ESOPHAGEAL CARCINOMA

Primary Tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma-in-situ

T1: Tumor invades lamina propria or submucosa

T2: Tumor invades muscularis propria

T3: Tumor invades adventitia

T4: Tumor invades adjacent structures

Regional Lymph Nodes (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Regional lymph node metastasis

DistantMetastasis (M)

MX: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis

Tumors of the lower thoracic esophagus

M1a: Metastasis in celiac lymph nodes

M1b: Other distant metastasis

Tumors of the mid-thoracic esophagus

M1a: Not applicable

M1b: Non regional lymph nodes and/or otherdistant metastasis

Tumors of the upper thoracic esophagus

M1a: Metastasis in cervical nodes

M1b: Other distant metastasis

Stage Grouping

Stage 0: TisN0M0

Stage I: T1N0M0

Stage IIA: T2N0M0

T3N0M0

Stage IIB: T1N1M0

T2N1M0

Stage III: T3N1M0

T4AnyNM0

Stage IV: AnyTAnyNM1

Stage IVA: AnyTAnyNM1a

Stage IVB: AnyTAnyNM1b